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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : C07D 417/04, 213/50 A61K 31/425, 31/44	A1	(11) International Publication Number: WO 93/15071
		(43) International Publication Date: 5 August 1993 (05.08.93)

(21) International Application Number: PCT/EP93/00176

(22) International Filing Date: 26 January 1993 (26.01.93)

(30) Priority data:
9201692.2 27 January 1992 (27.01.92) GB

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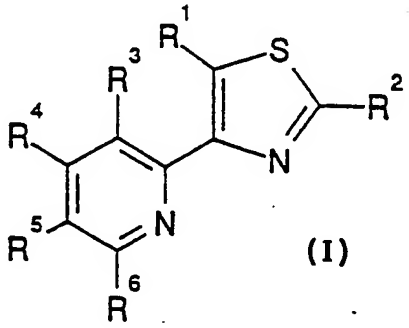
(81) Designated States: AU, CA, JP, KR, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: THIAZOLYL-PYRIDINE DERIVATIVES AND THEIR USE AS GASTRIC ACID SECRETION INHIBITORS



(I)

(57) Abstract

Pyridyl-thiazole derivatives, of structure (I), in which R^1 is optionally substituted phenyl; R^2 is C_{1-6}alkyl or $(CH_2)_nAr$ in which n is 0 to 2 and Ar is optionally substituted phenyl; R^3 is hydrogen or C_{1-4}alkyl; R^4 is hydrogen, C_{1-4}alkyl, NR^7R^8 or OC_{1-4}alkyl; R^5 is hydrogen or C_{1-4} alkyl; R^6 is hydrogen, C_{1-4}alkyl or NR^7R^8; R^7 and R^8 are the same or different and are each hydrogen or C_{1-4}alkyl or one of R^7 and R^8 is hydrogen and the other is hydroxy C_{1-4}alkyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 5- or 6-membered ring optionally containing one or more additional heteroatoms; or a salt thereof and their use in therapy as gastric acid secretion inhibitors.

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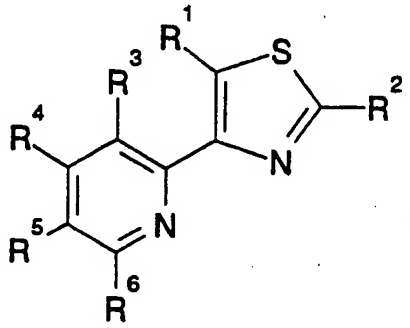
Thiazolyl-pyridine derivatives and their use as gastric acid secretion inhibitors

The present invention relates to novel substituted thiazole compounds, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them, and their use in therapy, in particular as gastric acid secretion inhibitors.

The present invention therefore provides, compounds of structure (I):



(I)

in which

R^1 is optionally substituted phenyl;

R^2 is C_{1-6}alkyl or $(CH_2)_nAr$ in which n is 0 to 2 and Ar is optionally substituted phenyl;

R^3 is hydrogen or C_{1-4}alkyl;

R_4 is hydrogen, C_{1-4}alkyl, NR^7R^8 or OC_{1-4}alkyl;

R^5 is hydrogen or C_{1-4} alkyl;

R^6 is hydrogen, C_{1-4}alkyl or NR^7R^8;

R^7 and R^8 are the same or different and are each hydrogen or C_{1-4}alkyl or one of R^7 and R^8 is hydrogen and the other is hydroxyC_{1-4}alkyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 5- or 6-membered ring optionally containing one or more additional heteroatoms;

and the salts thereof.

Suitably, R^1 is hydrogen or optionally substituted phenyl. Preferably R^1 is an optionally substituted phenyl group.

Suitable substituted phenyl groups R^1 include phenyl groups substituted by 1 to 3 substituents selected from C_{1-6}alkyl, C_{1-6}alkoxy, amino, C_{1-6}alkylthio, halogen, cyano, hydroxy, carbamoyl, carboxy, C_{1-6}alkanoyl or trifluoromethyl. Preferred substituted phenyl groups are those substituted by a single substituent, in particular a methyl group, most preferably in the 2-position of the ring.

Suitably, R^2 is C_{1-6}alkyl or $(CH_2)_nAr$; preferably R^2 is C_{1-6}alkyl, in particular n-propyl.

Suitably, n is 0 to 2, preferably n is 0 or 1.

Suitable substituted phenyl groups Ar are as defined for substituted phenyl groups R^1.

Suitably, R^3 is hydrogen or C_{1-4}alkyl; preferably R^3 is hydrogen.

Suitably R^4 is hydrogen, C_{1-4}alkyl, NR^7R^8 or OC_{1-4}alkyl; preferably R^4 is NR^7R^8.

Suitably R^5 is hydrogen or C_{1-4}alkyl; preferably R^5 is hydrogen.

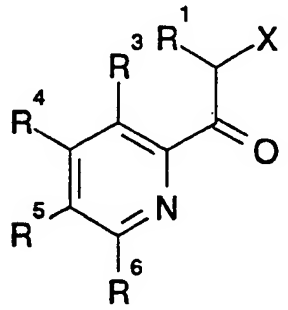
Suitably R^6 is hydrogen, C_{1-4}alkyl or NR^7R^8; preferably R^6 is hydrogen.

Suitably, R^7 and R^8 are the same or different and are each hydrogen or C_{1-4}alkyl or one of R^7 and R^8 is hydrogen and the other is hydroxyC_{1-4}alkyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 5- or 6-membered ring optionally containing one or more additional heteroatoms. Preferably R^7 and R^8 are the same and are both hydrogen.

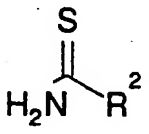
Suitable 5- or 6-membered rings formed by R^7 and R^8, together with the nitrogen atom to which they are attached, include, for example, pyrrolidino, morpholino, piperidino and piperazino rings.

The compounds of structure (I) can be prepared by processes analogous to those known in the art. The present invention provides in a further aspect a process for the preparation of a compound of structure (I) which comprises

a) reaction of a compound of structure (II) with a compound of structure (III):



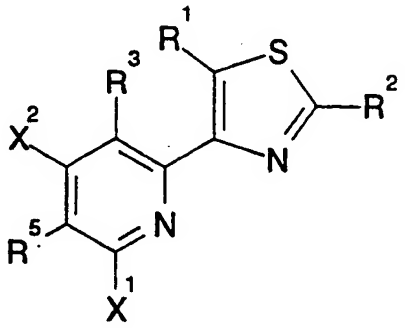
(II)



(III)

in which R^1 to R^6 are as described for structure (I), and X is halogen;

b) for compounds in which one of R^4 or R^6 is NR^7R^8, reaction of a compound of structure (IV):



(IV)

in which R^1, R^2, R^3 and R^5 are as described for structure (I) and one of X^1 and X^2 is halogen and the other is R^4 or

R^6 as appropriate, with a suitable amine of structure HNR^7R^8 in which R^7 and R^8 are as described for structure (I);

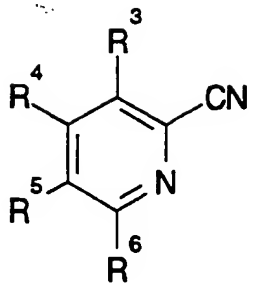
c) for compounds in which one of R^4 or R^6 is NH_2, reduction of a compound of structure (IV) in which X^1 or X^2 is N_3; and

optionally thereafter, forming a salt.

Suitably, X is halogen such as chlorine or bromine; preferably X is bromine. Suitably X^1 or X^2 is halogen such as chlorine or bromine; preferably X^1 or X^2 is chlorine.

The reaction between a compound of structure (II) and a compound of structure (III) is carried out in a suitable solvent at a temperature of between ambient and the reflux temperature of the solvent used, until the reaction is complete. Suitable solvents include, for example, C_{1-4}alkanols such as methanol and ethanol, in particular ethanol. Preferably the reaction is carried out at the reflux temperature of the solvent used.

Compounds of structure (II) can themselves be prepared according to procedures known to those skilled in the art. For example, compounds of structure (II) in which X is bromine, can be prepared from the corresponding precursors in which X is hydrogen, by reaction with, for example, bromine/hydrobromic acid at elevated temperature, preferably at reflux temperature, or with copper (II) bromide, in a suitable solvent medium (for example chloroform/ethyl acetate) at elevated temperature, preferably reflux temperature. The precursor compounds of structure (II) in which X is hydrogen, can be prepared from the corresponding 2-cyanopyridine of structure (V) and corresponding Grignard reagent (VI):



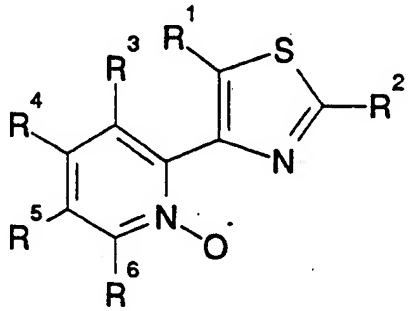
(V) R^1CH_2MgX (VI)

in which R^1 and R^3 to R^6 are as described for structure (I) and X is halogen.

The starting compounds of structures (V) and (VI) are commercially available or can be prepared by standard techniques from commercially available precursors.

The reaction between compounds of structure (IV) and suitable amines of structure HNR^4R^5 can be carried out in a suitable solvent such as industrial methylated spirits, at elevated temperature, preferably under pressure, for example in a sealed pressure vessel at elevated temperature.

The intermediate compounds of structure (IV) are prepared by standard techniques, for example, by reaction of the corresponding pyridine-N-oxides (VII) with, for example phosphorous oxychloride.



(VII)

The reduction of compounds of structure (IV) in which X^1 is azide is carried out by hydrogenation over a noble metal catalyst, such as palladium on carbon. The intermediates of structure (IV) in which X^1 is azide can be

prepared from the corresponding compounds of structure (VII) by reaction with $(PhO)_2P(O)N_3$.

The intermediates of structure (VII) can be prepared from the corresponding compounds of structure (I) in which R^3 to R^6 are all hydrogen, by reaction with a suitable oxidising agent such as m-chloroperbenzoic acid.

The compounds of structure (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal H^+K^+ATPase enzyme (Fellenius, E., Berglindh, T., Sachs, G., Olke, L., Elander, B., Sjostrand, S.E., and Wallmark, B., 1981, Nature, 290, 159-61).

In a further aspect therefore the present invention provides compounds of structure (I) and pharmaceutically acceptable salts thereof for use in therapy. The compounds of structure (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are useful in the treatment of gastrointestinal diseases in mammals, in particular humans.

Such diseases include, for example, gastric and duodenal ulcers, aspiration pneumonitis and Zollinger-Ellison Syndrome.

Further, the compounds of structure (I) can be used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, acute upper intestinal bleeding, in patients with a history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition. The present invention

therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone,

lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains suitably from 1 to 1000 mg, preferably from 1 to 500 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The present invention also provides a method of inhibiting gastric acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof; and a method of treatment of diseases of the stomach or intestine based on increased acid secretion which comprises administering to a mammal in need thereof an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

The pharmaceutically acceptable compounds of the invention will normally be administered to a subject for the treatment of gastrointestinal diseases and other conditions caused or exacerbated by gastric acidity. The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 1000 mg, preferably between 1 mg

and 500 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day.

Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

In addition, the compounds of the present invention can be co-administered with further active ingredients, such as antacids (for example magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-flammatory drugs (for example indomethacin, aspirin or naproxen), steroids, or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example histamine H_2-antagonists such as cimetidine), or agents having activity against Helicobacter pylori organisms, for example antibiotics such as amoxicillin.

The following examples illustrate the invention. Temperatures are recorded in degrees centigrade.

Exampl 1

2-Propyl-4-(2-pyridyl)-5-(2-methylphenyl)thiazole dihydrobromide

(i) 2-(2-Methylphenylacetyl)pyridine

A solution of α-bromo-o-xylene (9.25 g, 0.05 mol) in anhydrous ether (50 ml) was added dropwise under nitrogen to a stirred mixture of magnesium turnings (1.21 g, 0.05 mol) and anhydrous ether (15 ml) so as to maintain a gentle reflux. After a further 10 min, a solution of 2-cyano-pyridine (5.2 g, 0.05 mol) in anhydrous ether (50 ml) was added dropwise over 15 min. The mixture was stirred for a further 2 hours, left to stand for 16 hours, then cooled in ice and a 20% aqueous ammonium chloride solution added dropwise, followed by conc. hydrochloric acid (14 ml) to give two clear layers. The aqueous layer was separated and extracted with chloroform. The combined organic layers were dried and evaporated to a dark oil, which was purified by flash chromatography (silica, dichloromethane) to give the title compound as an oil (4.86 g).

(ii) 2-(2-Methylphenylbromoacetyl)pyridine

A solution of 2-(2-methylphenylacetyl)pyridine (21.26 g, 0.1 mol) in 48% aqueous hydrobromic acid (100 ml) was heated at 100 °C whilst bromine (17.7 g. 0.11 mol) was added dropwise over 5 min. After a further 10 min the solution was allowed to cool, and the resulting solid filtered off and washed with acetonitrile, then converted to the free base and crystallised from pet. ether to give the product (15.88 g), m.p. 53-55°C.

(iii) 2-Propyl-4-(2-pyridyl)-5-(2-methylphenyl)thiazole dihydrobromide

A solution of 2-(2-methylphenylbromoacetyl)pyridine (1.82 g, 6.27 mmol) and thiobutyramide (0.65 g, 6.27 mmol) in ethanol

(40 ml) was heated under reflux for 4 hours. The solvent was evaporated and the residue triturated with ether, slowly giving a crystalline solid. Conversion to the dihydrobromide and recrystallisation from ethanol/ether then from methanol/ether gave the title compound as a yellow solid (1.25 g), m.p. 200-201°C.

$C_{18}H_{18}N_2S \cdot 2HBr$

Found	C 47.28, H 4.46, N 6.05, Br 34.72, S 6.83
Requires	C 47.39, H 4.42, N 6.14, Br 35.03, S 7.03

Example 2

2-Propyl-4-(6-methylamino-2-pyridyl)-5-(2-methylphenyl)thiazole

(i) 2-Propyl-4-(1-oxo-2-pyridyl)-5-(2-methylphenyl)thiazole

2-Propyl-4-(2-pyridyl)-5-(2-methylphenyl)thiazole dihydrobromide (10.74 g, 28.6 mmol) was converted to the free base by treatment with sodium bicarbonate and extraction into dichloromethane. *m*-Chloroperbenzoic acid (55.93 g, 34.4 mmol) was added to the organic solution portionwise over about 5 min with stirring. The clear solution was left to stand for 16 hours, then cooled in ice, ammonia gas bubbled through, the precipitate filtered off and the filtrate evaporated to a brown oil. Flash chromatography (silica, methanol/dichloromethane) and crystallisation from pet. ether gave the title compound (6.87 g), m.p. 80-82°C.

(ii) 2-Propyl-4-(6-chloro-2-pyridyl)-5-(2-methylphenyl)-thiazole and 2-propyl-4-(4-chloro-2-pyridyl)-5-(2-methylphenyl)thiazole

2-Propyl-4-(1-oxo-2-pyridyl)-5-(2-methylphenyl)thiazole (2.15 g, 6.93 mmol) and phosphoryl chloride (5 ml, excess) were heated at 120 °C for 1 hour. The excess phosphoryl chloride was evaporated, and the residue treated with ice-water, basified with sodium bicarbonate and extracted with dichloromethane, then the extracts dried and evaporated.

Chromatography (silica, dichloromethane/methanol) gave 2-propyl-4-(6-chloro-2-pyridyl)-5-(2-methylphenyl)thiazole as a low-melting solid (1.19 g), m.p. 64-66°C, and 2-propyl-4-(4-chloro-2-pyridyl)-5-(2-methylphenyl)thiazole as an oil (0.62 g).

(iii) 2-Propyl-4-(6-methylamino-2-pyridyl)-5-(2-methylphenyl)thiazole

2-Propyl-4-(6-chloro-2-pyridyl)-5-(2-methylphenyl)thiazole (2.0 g, 6.1 mmol) and a 33% solution of methylamine in IMS (50 ml) were heated together in a pressure vessel at 185 °C for 16 hours. After cooling, the solvent was evaporated, the residue treated with dilute aqueous sodium carbonate solution, and extracted several times with dichloromethane. The combined extracts were dried and evaporated to an oil, which was purified by flash chromatography (silica, dichloromethane/methanol) to give the title compound (1.21 g) as an oil.

$C_{19}H_{21}N_2S$

Found	C 70.49, H 6.38, N 12.93
Requires	C 70.55, H 6.54, N 12.99

Example 3

2-Propyl-4-(6-(2-hydroxyethylamino)-2-pyridyl)-5-(2-methylphenyl)thiazole

2-Propyl-4-(6-chloro-2-pyridyl)-5-(2-methylphenyl)thiazole (1.0 g, 3.04 mmol) and ethanolamine (5 ml, excess) were heated under reflux for 16 hours. The solution was diluted with water and extracted several times with dichloromethane. The combined extracts were washed with water, dried and evaporated to an oil, which was purified by flash chromatography (silica, dichloromethane/methanol), then crystallisation from acetone/water to give the title compound (0.69 g) as a hydrate, m.p. indeterminate.

$C_{20}H_{23}N_3OS \cdot 1.27H_2O$

Found C 63.85, H 6.77, N 11.06

Requires C 63.82, H 6.84, N 11.17

Example 4

2-Propyl-4-(6-amino-2-pyridyl)-5-(2-methylphenyl)thiazole

(i) 2-Propyl-4-(6-azido-2-pyridyl)-5-(2-methylphenyl)-thiazole

2-Propyl-4-(1-oxo-2-pyridyl)-5-(2-methylphenyl)thiazole (2.0 g, 6.44 mmol) and diphenylphosphoryl azide (3.55 g, 12.9 mmol) were heated at 155-160°C for 3 hours. After cooling, the residue was treated with aqueous sodium hydroxide and extracted with dichloromethane. The extracts were dried and evaporated to an oil, which was purified by flash chromatography (silica, ether/pet. ether) and crystallisation from ether/pet. ether to give the title compound (0.38 g), m.p. 70-72°C.

(ii) 2-Propyl-4-(6-amino-2-pyridyl)-5-(2-methylphenyl)-thiazole

A solution of 2-propyl-4-(6-azido-2-pyridyl)-5-(2-methylphenyl)thiazole (0.5 g, 1.5 mmol) in ethanol (50 ml) was hydrogenated over 10% palladium on charcoal (0.1 g) at 50 p.s.i. for 2.5 hours. The catalyst was filtered off and the filtrate evaporated. Recrystallisation from ether/ pet. ether gave the title compound (0.22 g), m.p. 80-81°C.

$C_{18}H_{19}N_3S$

Found C 69.91, H 6.25, N 13.58

Requires C 69.87, H 6.19, N 13.58

Example 5

2-Propyl-4-(4-amino-2-pyridyl)-5-(2-methylphenyl)thiazole

2-Propyl-4-(4-chloro-2-pyridyl)-5-(2-methylphenyl)thiazole (0.62 g, 1.88 mmol) and phenol (8g, excess) were heated with

stirring at 200 °C, whilst ammonia gas was bubbled through for 3 hours. The excess phenol was distilled off under reduced pressure, and the residue treated with aqueous sodium hydroxide and extracted with ether. The combined extracts were dried and evaporated to an oil, which was purified by flash chromatography (silica, methanolic ammonia/dichloromethane) then crystallised from pet. ether to give the title compound (0.2 g), m.p. 135-136°C.

$C_{18}H_{19}N_3S$

Found	C 69.73, H 6.17, N 13.45
Requires	C 69.87, H 6.19, N 13.58

Example 6

2-Methyl-4-(2-pyridyl)-5-(2-methylphenyl)thiazole hydrobromide

A solution of 2-(2-methylphenylbromoacetyl)pyridine (1.3 g, 4.48 mmol) and thioacetamide (0.4 g, 5.4 mmol) in ethanol (25 ml) was heated under reflux for 5 hours. The solvent was evaporated and the residue triturated with ether to give a yellow solid which after recrystallisation from methanol/acetone then from acetonitrile gave the title compound (0.56 g), m.p. 209-212°C.

$C_{16}H_{14}N_2S \cdot HBr$

Found	C 55.37, H 4.35, N 8.13
Requires	C 55.34, H 4.35, N 8.07

Example 7

2-(2-Methylphenyl)-4-(2-pyridyl)-5-(2-methylphenyl)thiazole hydrobromide

A solution of 2-(2-methylphenylbromoacetyl)pyridine (0.7 g, 2.41 mmol) and 2-methylthiobenzamide (0.44 g, 2.89 mmol) in ethanol (15 ml) was heated under reflux for 4 hours. The solvent was evaporated and the residue triturated with ether to give a yellow solid which after recrystallisation from acetonitrile gave the title compound (0.51 g), m.p. 221-223°C.

	$C_{22}H_{18}N_2S \cdot HBr$
Found	C 62.05, H 4.58, N 6.70
Requires	C 62.41, H 4.52, N 6.62

Example 8

2-(Phenylmethyl)-4-(2-pyridyl)-5-(2-methylphenyl)thiazole

A solution of 2-(2-methylphenylbromoacetyl)pyridine (1.03 g, 3.55 mmol) and phenylthioacetamide (0.64 g, 4.26 mmol) in ethanol (20 ml) was heated under reflux for 4 hours. The solvent was evaporated and the residue treated with aqueous sodium bicarbonate and extracted with dichloromethane. Drying and evaporation of the organic layer followed by flash chromatography (silica, dichloromethane/ethyl acetate) and crystallisation from pet. ether gave the title compound (0.86 g), m.p. 94-95°C.

	$C_{22}H_{18}N_2S$
Found	C 77.21, H 5.33, N 8.27
Requires	C 77.16, H 5.30, N 8.18

Example 9

2-Propyl-4-(2-pyridyl)-5-ph nylthiazole hydrobromide

(i) 2-(Phenylbromoacetyl)pyridine

To a stirring solution of 2-phenylacetylpyridine (5.0 g, 0.025 mol) in conc. HBr (48-50% w/w, 25 ml) at 100°C was added bromine (1.42 ml, 0.0275 mol) dropwise over a period of 5 mins. The solution was maintained at 100°C for a further 10 mins then cooled to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were washed with dilute sodium bicarbonate, dried and evaporated to an oil which was crystallised from petroleum ether to give the title compound (4.25 g) m.p. 54-55°C.

(ii) 2-Propyl-4-(2-pyridyl)-5-phenylthiazole

2-(Phenylbromoacetyl)pyridine (4.0 g, 0.0145 mol) and thiobutyramide (1.79 g, 0.0174 mol) were dissolved in ethanol (50 ml) and refluxed for 4 hrs. The solvent was evaporated off and the residue triturated with ether to give buff coloured crystals. These were filtered off, recrystallised from acetonitrile/ether and dried to yield the title compound (2.58 g), m.p. 130-133°C.

$C_{17}H_{16}N_2S \cdot HBr$

Found: C 56.05 H 4.76 N 7.83

Requires: C 56.51 H 4.74 N 7.75

Bi logical Data.

H^+K^+ATPase Activity.

The effects of a single high concentration (100 μM) of a compound of structure (I) on K-stimulated ATPase activity in lyophilised gastric vesicles was determined. Preferred compounds of structure (I) were also tested over a range of concentrations to determine IC_{50} values.

(i) Preparation of lyophilised gastric vesicles (H/K-ATPase).

Lyophilised gastric vesicles were prepared from pig fundic mucosa after the method of Keeling et. al. (Biochem. Pharmacol., 34, 2967, 1985).

(ii) K^+-stimulated ATPase activity.

K^+-stimulated ATPase activity was determined at 37°C in the presence of the following : 10 mM Pipes/Tris buffer pH 7.0, 2 mM $MgSO_4$, 1 mM KCl, 2 mM Na_2ATP and 3-6 μg protein/ml lyophilised gastric vesicles. After incubation for 30 minutes, the inorganic phosphate hydrolysed from ATP was determined by the method of Yoda and Hokin (Biochem. Biophys. Res. Commun. 40, 880, 1970).

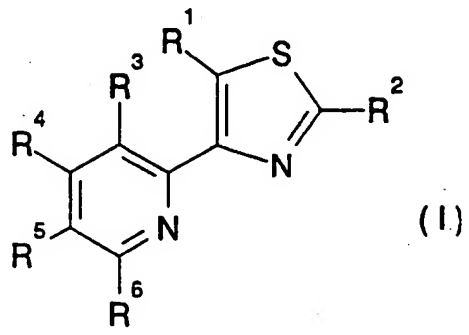
Compounds of structure (I) were dissolved in dimethylsulphoxide which up to the highest concentration used had no effect on K^+-stimulated ATPase activity. The effect of the highest concentration of each compound of structure (I) on the recovery of a standard amount of inorganic phosphate was also determined.

Results

The compounds of the examples exhibited IC_{50} values in the range of between 1 and 100 μM.

Claims:

1. A compound of structure (I):



(I)

in which
R^1 is optionally substituted phenyl;
R^2 is C_{1-6}alkyl or $(CH_2)_nAr$ in which n is 0 to 2 and Ar is optionally substituted phenyl;
R^3 is hydrogen or C_{1-4}alkyl;
R_4 is hydrogen, C_{1-4}alkyl, NR^7R^8 or OC_{1-4}alkyl;
R^5 is hydrogen or C_{1-4} alkyl;
R^6 is hydrogen, C_{1-4}alkyl or NR^7R^8;
R^7 and R^8 are the same or different and are each hydrogen or C_{1-4}alkyl or one of R^7 and R^8 is hydrogen and the other is hydroxyC_{1-4}alkyl, or R^7 and R^8, together with the nitrogen atom to which they are attached, form a 5- or 6-membered ring optionally containing one or more additional heteroatoms;
or a salt thereof.

2. A compound according to claim 1 in which R^1 is o-methylphenyl.

3. A compound according to claim 2 in which R^2 is n-propyl.

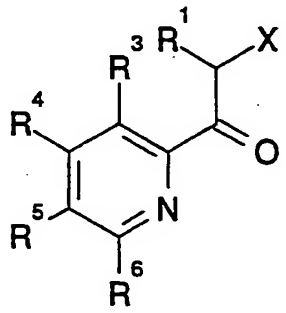
4. A compound according to claim 3 in which R^3 is NR^7R^8 in which R^7 and R^8 are both hydrogen.

5. A compound of structure (I) which is:

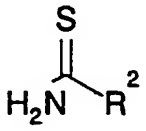
2-propyl-4-(2-pyridyl)-5-(2-methylphenyl)thiazole dihydrobromide;
2-propyl-4-(6-methylamino-2-pyridyl)-5-(2-methylphenyl)-thiazole;
2-propyl-4-(6-(2-hydroxyethylamino)-2-pyridyl)-5-(2-methylphenyl)thiazole;
2-propyl-4-(6-amino-2-pyridyl)-5-(2-methylphenyl)thiazole;
2-propyl-4-(4-amino-2-pyridyl)-5-(2-methylphenyl)thiazole;
2-methyl-4-(2-pyridyl)-5-(2-methylphenyl)thiazole hydrobromide;
2-(2-methylphenyl)-4-(2-pyridyl)-5-(2-methylphenyl)-thiazole;
2-(phenylmethyl)-4-(2-pyridyl)-5-(2-methylphenyl)thiazole; or
2-propyl-4-(2-pyridyl)-5-phenylthiazole hydrobromide.

6. A process for preparing a compound of structure (I) which comprises

a) reaction of a compound of structure (II) with a compound of structure (III):



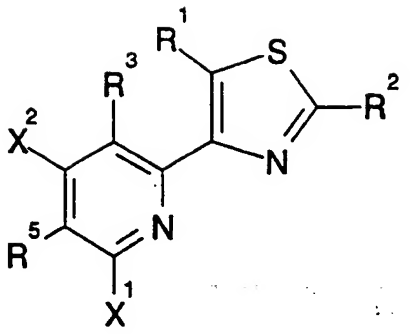
(II)



(III)

in which R^1 to R^6 are as described for structure (I), and X is halogen;

b) for compounds in which one of R^4 or R^6 is NR^7R^8, reaction of a compound of structure (IV):



(IV)

in which R^1, R^2, R^3 and R^5 are as described for structure (I) and one of X^1 and X^2 is halogen and the other is R^4 or R^6 as appropriate, with a suitable amine of structure HNR^7R^8 in which R^7 and R^8 are as described for structure (I);

c) for compounds in which one of R^4 or R^6 is NH_2, reduction of a compound of structure (IV) in which X^1 or X^2 is N_3; and

optionally thereafter, forming a salt.

7. A pharmaceutical composition comprising a compound according to any one of claims 1 to 5 or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

8. A compound according to any one of claims 1 to 5 for use in therapy, in particular in the treatment of gastrointestinal disorders.

9. A compound of structure (II) as defined in claim 6.

10. A compound of structure (IV) as defined in claim 6.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/00176

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D417/04; C07D213/50; A61K31/425; A61K31/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 149 884 (TAKEDA CHEMICAL INDUSTRIES) 31 July 1985 see claims 1-3,8 ---	1,7,8
A	EP,A,0 169 502 (MERCK AND CO.) 29 January 1986 see claims 1,4 ---	1,7
A	EP,A,0 325 496 (SUMITOMO PHARMACEUTICALS COMPANY LIMITED) 26 July 1989 see claims 1,14,21 ---	1,7,8

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
22 MARCH 1993	19. 04. 93
International Searching Authority	**Signature of Authorized Officer**
EUR PEAN PATENT OFFICE	HENRY J.C.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JOURNAL OF HETEROCYCLIC CHEMISTRY. vol. 22, no. 3, May 1985, PROVO US pages 669 - 671 WALTER KLOSE ET AL 'Synthese von Pyridylphenyl-imidazo[2,1-b]thiazolen' *page669,compound 7;page 670,compound 7a*	9

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9300176
SA 70313

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 22/03/93

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		JP-A- 60058981	05-04-85
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		AU-A- 3243384	14-03-85
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		US-A- 5021435	04-06-91

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